A minimal stochastic model for influenza evolution

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We introduce and discuss a minimal individual-based model for influenza dynamics. The model takes into account the effects of specific immunization against viral strains, but also infectivity randomness and the presence of a short-lived strain transcending immunity recently suggested in the literature. We show by simulations that the resulting model exhibits substitution of viral strains along the years, but that their divergence remains bounded. We also show that dropping any of these features results in a drastically different behavior, leading either to the extinction of the disease, to the proliferation of the viral strains, or to their divergence.

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I. INTRODUCTION

Influenza [1] exhibits two apparently contradictory features: on the one hand, any given individual can get infected with the disease over and over again, since the virus mutates fast enough to escape acquired immunity; on the other hand, on any given epidemic season, the viral strain is sufficiently well-defined, so that an effective vaccine can be identified. The fact that circulating viral strains are closely related is also exhibited by the shape of its phylogenetic trees [2, 3]. Influenza A, the most relevant epidemiologically, can be distinguished in several subtypes, according to the nature of their capside proteins hemagglutinin (H) and neuroaminidase (N). The currently prevailing strains belong to the H3N2 subtype. The phylogenetic relationships of different strains within a subtype are usually reconstructed from the hemagglutinin (HA) sequences, since this protein appears to be highly prone to substitutions. The resulting tree has a characteristic comb-like shape, with a well-defined backbone and several short-lived side branches. This has been contrasted with the trees of other viruses, like HIV or the measles virus, which show more ramified patterns [4].

This problem has been recently addressed by Ferguson et al. [5], who identified a short-term strain-transcending immunity as the essential factor to avoid the dichotomy between extinction and strain proliferation, and obtained phylogenetic trees quite similar to the one observed. However, the model proposed in ref. [5] contains a very high number of parameters, including a nontrivial source of heterogeneity among individuals in the geographic pattern of transmission.

We build up in this paper what we believe is a minimal model explaining this feature of influenza epidemiology within a subtype. The model takes into account the genetic drift of the virus and the effects of specific immunization. It also features a short-term cross-immunity effective against all viral strains (*short immunity*), introduced in ref. [5], and the competition between viral strains, not previously considered, due to their different infectivities. The possible relevance of such an effect is supported by a recent study [6] which shows that single-nucleotide substitutions can lead to large fitness changes in RNA viruses. The removal of any of these features from the model would impair its viability.

In section II we provide a brief review of recent models describing the dynamics of influenza. In section III we describe the model we propose. An analysis of its behavior and the simulation results are expounded in section IV. We close by a discussion of our results and an outlook on further research.

II. MODELS OF INFLUENZA DYNAMICS

Recent models of influenza dynamics combine the classical ideas of mathematical epidemiology with aspects of evolutionary genetics. In a class of models, represented, e.g., by [7, 8, 9, 10], one assumes the existence of a single preferred strain at each season, at a given genetic distance from the previously preferred one. These models show how the virus population can drift fast enough to remain close to the preferred strain: however, they do not address the crucial question mentioned above, namely the quasi-one dimensional structure of phylogenetic tree.

In a second class of models [11, 12, 13] the genetic drift of the virus is assumed to take place in a low-dimensional space ($d = 1, 2$) with only one viable mutation resolving the compromise of maintaining the effectiveness of the HA protein and escaping the detection by the immune system. These models can be studied quite deeply with combined analytical and numerical methods. They exhibit a regime with travelling waves, describing a persist-

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ing genetic drift of the virus with a bounded diversity. Although from a pragmatic point of view these models provide a reasonable representation of the observations, directionality in evolution is assumed rather than derived. This has different problems: Simple stochastic variations of the model do not lead to the desired behavior. A stochastic process that has on average only one escape direction at a given time would face extinction after a finite number of steps. Moreover, a detailed analysis of HA sequences in ref. [14, 15] identifies a non trivial structure of clusters that succeed one another in time with abrupt jumps in protein Hamming distance from one cluster to another. This gives circumstantial evidence that a larger than one-dimensional manifold in genomic space is involved in the process.

The most structured attempt to derive a working model of interaction between viral strain evolution and epidemiological dynamics is represented by ref. [5]. In this model a complex spatial structure of the host population as well as a detailed parametrization of the dynamics of infection and recovery is introduced, and the viral evolution takes place in a high-dimensional genomic space. The main result of the authors is that in order to avoid the proliferation of strains it is necessary to assume that infection to a given virus, in addition to conferring long term specific immunity to close strains, it also elicits a *short immunity* against all possible variants. Unfortunately the models contains a high number of parameters and it is difficult to isolate this mechanism from the different details of the model.

III. BUILDING UP THE MODEL

We use an individual-based model generalizing the bit-string model introduced in ref. [11]. We consider a population of N individuals, which can be host to the virus. The antigenic features of the virus are summarized in a binary string σ of length L. Each host can be in one of the following states:

Healthy: The host can be infected by suitable strains of the virus, depending on its acquired immunity;

Infected: The host is infected by a unique viral strain σ;

Recovered: The host is not infected and cannot be infected by any viral strain. This state represents those individuals which are protected by the *short immunity* against infection by any influenza strain.

The immunity acquired by any host i in its lifetime is described by the temporally ordered set Σ_i of strains which have infected it in the past. A viral strain σ cannot infect a host i if the set Σ_i contains one or more strains σ' such that the Hamming distance $d_{\rm H}(\sigma,\sigma') \leq r$, where r is the immunity range. Individuals are removed with rate λ^{-1}, independently of their state (where λ is the average lifetime), and replaced by healthy individuals with a virgin immune state ($\Sigma = \emptyset$). Similarly, the duration of the illness and that of the recovered state are exponentially distributed with averages τ and η respectively. The memory set Σ_i has a maximal length ℓ_0. If an individual has been infected by more than ℓ_0 strains, only the most recent ℓ_0 ones are remembered. Since at any given time "too old" variants are completely extinct and out of the immunity range relative to the active ones, the dynamics of the model is independent of ℓ_0 if this parameter is large enough. We have used $\ell_0 = 50$ in the simulations, but independence is already reached for $\ell_0 \simeq 20$. The recovered state represents the *short immunity* introduced by Ferguson et al. [5]. The disease is transmitted through random encounters between infected and healthy individuals, assuming homogeneous mixing, in the dynamical process that we now describe.

At each time step (representing a duration $\mathrm{d}t/N$) an individual i is picked up at random. If the individual is infected, one first checks for possible mutations of the virus: with probability $\mu \mathrm{d}t$ the state of one of the bits of its strain σ_i is changed. Then one picks up at random ν different individuals in the population, where ν is Poisson distributed with average $\beta(\sigma_i)\mathrm{d}t/\tau$, where $\beta(\sigma_i)$ is the infectivity of the viral strain σ_i. If one of these individuals is healthy, and its immune memory does not elicit immunity, it becomes infected with strain σ_i. Then, with probability $\mathrm{d}t/\tau$, the individual i goes to the recovered state, and the strain σ_i is added to its immune memory Σ_i. If the individual i is recovered, then it moves to the healthy state with probability $\mathrm{d}t/\eta$. The infectivities $\beta(\sigma)$ are assumed to be independent, identically distributed random variables for each strain σ, with a gamma distribution of average β_0 and parameter k:

$$p(\beta; k, \beta_0) \propto \left(\frac{k\beta}{\beta_0}\right)^{k-1} \mathrm{e}^{-k\beta/\beta_0}. \qquad (1)$$

The gamma distribution has the advantage of being easy to implement and of being naturally defined only for non-negative values of β.

The values of the parameters are chosen to be close to realistic estimates. One of the problems we meet is to consider populations large enough to avoid extinctions due to stochastic fluctuations, and to reasonably implement the immune memory. We could simulate in reasonable time systems of size up to $N = 500000$. We choose the year as unit of time and set the average duration τ of the illness to 0.02 (i.e., roughly one week). We set the average duration η of the recovered state as 0.75 (i.e, after 6 months one has $\sim 50\%$ probability of being no more immune).

According to ref. [16], the spontaneous genomic mutation rate $\mu_{\rm g}$ for influenza A viruses equals roughly one mutation per genome per replication. Taking into account the duration of a viral generation (a few hours) and the fact that we are looking at a small portion of the genome ($L = 32$ in the simulations that follow) we can set $\mu \simeq 1$ per strain per year as a good order of magnitude.

We implemented two versions of this model, that differ by the duration of the elementary time step. This difference affects the details of the dynamics, but not the overall behavior of the model. In the slow version, the elementary time step $\mathrm{d}t$ was taken as small as 0.001, i.e., about 8 hours. In the fast version, we took $\mathrm{d}t = \tau$ (the duration of the illness), i.e., at the end of the infection process, the infected individual was systematically moved to the recovered state. The fast version was used to explore the phase space of the model, and the behavior of the system in the interesting regime was then analyzed in details with the slow version.

IV. RESULTS

We first look at the simple version of the model, in which the duration of the recovered state is negligible, and the infectivity β is not random. This model coincides with the bitstring model introduced by Girvan et al. [11], and exhibits only two possible behaviors: extinction of the viral disease, or proliferation of the viral strains. We show in fig. 1 the results of the simulation of the model with a population of 500000 individuals.

All results quoted in this explorative stage were obtained with the fast version of the dynamics.

An important parameter characterizing the viral population at a given time is the effective number of circulating strains n,defined as the inverse participation ratio of the numbers ν_σ of individuals infected by strain σ, namely

$$n = \left(\sum_\sigma \nu_\sigma\right)^2 \Big/ \left(\sum_\sigma \nu_\sigma^2\right). \tag{2}$$

Since due to mutations one can have many different strains, each infecting only a small number of individuals, the effective number of strains can be much smaller than the total one. We also monitored some quantities which could give us some insight into the way the viral strains explore sequence space. The system is initialized with a single viral strain $\sigma = \sigma_0 = (0, 0, \ldots, 0)$, and mutations set to 1 some of these zeros. We could thus evaluate, at least initially, the drift of the strain, by computing the average of the Hamming distance of the active strains from the initial point:

$$\Delta_\mathrm{H} = \frac{1}{I}\sum_\sigma d_\mathrm{H}(\sigma, \sigma_0)\,\nu_\sigma. \tag{3}$$

Here I is the incidence of the disease, i.e., the total number of infected:

$$I = \sum_\sigma \nu_\sigma. \tag{4}$$

We call "active" strains those for which $\nu_\sigma > 0$. On the other hand, the cloud of active viral strains broadens as it drifts. Its width can be estimated by evaluating the average mutual Hamming distance between active strains, weighted by their incidence:

$$\delta_\mathrm{H} = \frac{2}{I(I-1)}\sum_{(\sigma,\sigma')} d_\mathrm{H}(\sigma, \sigma')\,\nu_\sigma\nu_{\sigma'}, \tag{5}$$

where the sum runs over all distinct pairs (σ, σ') of active strains.

It is interesting that in this regime, as already noticed in ref. [11], the disease gets extinct at large values of the infectivity. With our data, e.g., for $r = 2$, $\mu = 1$, extinction occurs for $\beta_0 < 2$, but also for $\beta_0 > 8$. This effect is due to the fact that the initial ripple in the number of infected individuals is followed by a severe bottleneck, as shown in fig. 1. The bottleneck becomes more intense as the infectivity increases, eventually leading to extinction. The eventual proliferation of viral strains makes it difficult to analyze this model by generalizing the occupation number representation framework used, e.g., in [12] to a multidimensional sequence space [17].

Since this model cannot sustain the nonproliferating strain regime characteristic of influenza, we considered if infectivity randomness alone could be responsible for it. Indeed, recent studies [6] have shown that single-nucleotide substitutions lead to a wide distribution of fitness effects in an RNA virus. It is likely that some of these effects also arise in the short nucleotide sequence coding for the immunologically relevant section of NA. We have thus attached to each strain σ a value β_σ of the infectivity, drawn from a gamma distribution of average β_0 and parameter k.

The behavior of the system in the presence only of the randomly distributed infectivity does not appear much different from that of the simple bitstring model. There are only the proliferation and the extinction regimes. If anything, the phase space allotted to the proliferating regime is reduced, because the high average values of the infectivity. The illness did not appear to remain, with our mutation rate and population size, for ranges $r \geq 3$. The average infectivity values in the population appear much larger than the average β_0 of the distribution, suggesting that the competition takes place at the tail of the distribution. This behavior does not depend strongly on the parameter k, although the average values of the infectivity become smaller as k is increased.

If the infectivity is nonrandom, but the short-term general immunity is present, the disease either dies off or, after a few ripples, reaches a steady state at an incidence level (number of infected) of the order of

$$I^* = N\frac{\tau}{\tau+\eta}\left(1 - \frac{1}{\beta_0}\right). \tag{6}$$

In this regime, however, the effects of specific immunization are apparent only in the small reduction of the steady-state incidence level, as seen in fig. 3, left. On the other hand, one can see in fig. 3 that the effective number of active strains remains high, and most of all that they

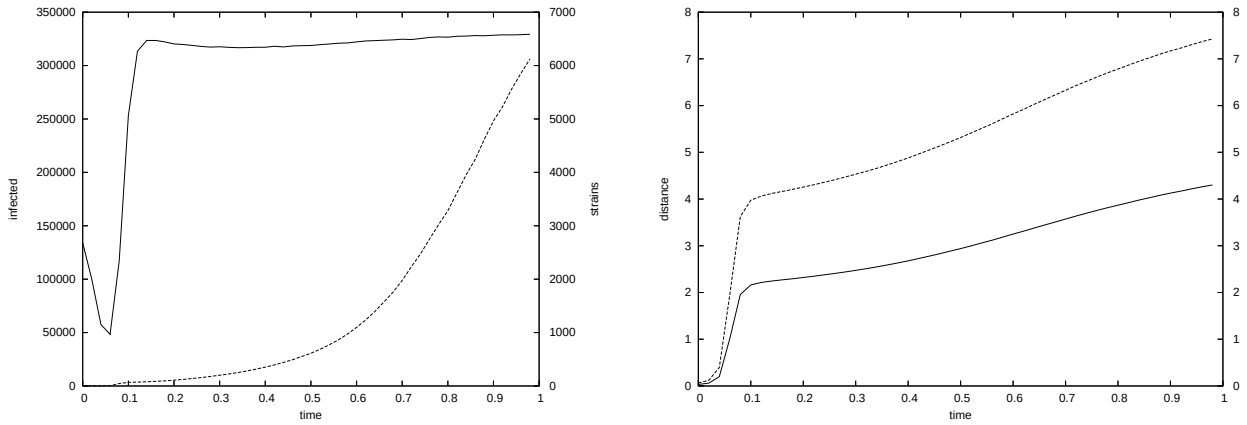

FIG. 1: Simulation of the bitstring model with 500000 individuals. Parameters: duration of the illness $\tau = 0.02$, lifetime $\lambda = 50$, infectivity $\beta = \beta_0 = 3$, immunity range $r = 1$. Left: Continuous line (left axis): number of infected as a function of time. Dashed line (right axis): effective number of strains vs. time. Right: Continuous line: Average Hamming distance of the active strains from the origin. Dashed line: Average Hamming distance between active strains.

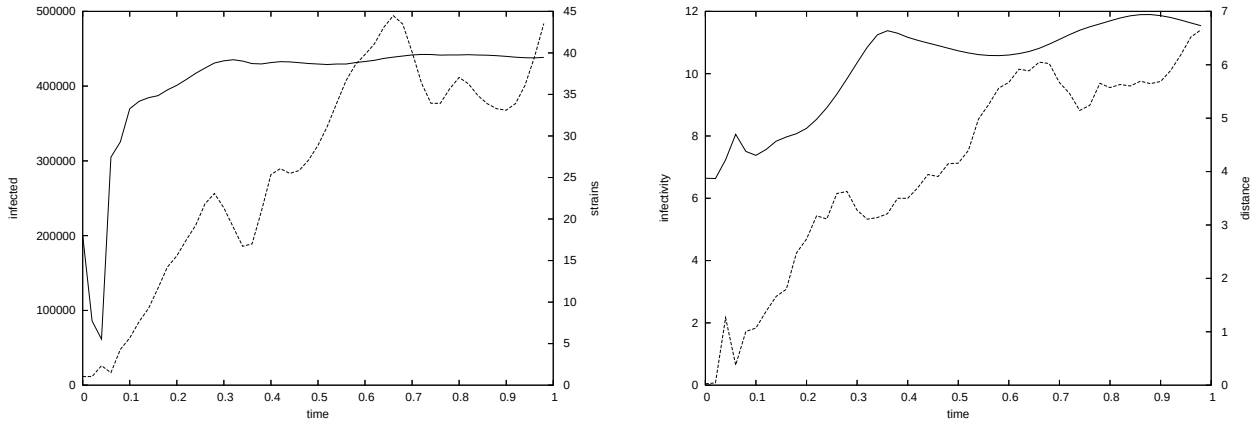

FIG. 2: Behavior of the system with randomly distributed infectivity. Expected value of the infectivity $\beta_0 = 3$, parameter $k = 3$, other parameters as in fig. 1. Left: Continuous line (left axis): Number of infected vs. time. Dashed line (right axis): Effective number of strains. Right: Continuous line (left axis): Average value of the infectivity. Dashed line (right axis): Average Hamming distance among active strains. Notice the proliferation and the divergence of the strains.

diverge so that the average Hamming distance soon gets close to the theoretical value for a random sample.

The picture changes if *both* random infectivity and short immunity are introduced. We show in fig. 4 the behavior of the system with short immunity of duration 0.75 years, and gamma-distributed infectivity with parameter $k = 3$ and an expected value $\beta_0 = 3$. Although the incidence of the disease settles down to a level close to the stationary level dictated by eq. (6), one can see that the effective number of strains remains of order unity. The competition among viral strains shows up quite clearly in the oscillating behavior of $n(t)$ and of $\delta_{\mathrm{H}}(t)$. One can see that the actual average values of the infectivity remain quite high and that, in spite of the ongoing competition, the incidence of the disease does not show pronounced oscillations.

We can now consider the slow version of the program, in order to analyze the behavior of the model in details. We show in fig. 5 the results of a simulation in which the time interval $\mathrm{d}t$ is taken equal to 10^{-3} years (corresponding to a few hours), and the other parameters are as in fig. 4, apart from the genome length L, which is set equal to 128 in order to reduce the probability of back mutations. While the overall incidence level remains close to that previously obtained, one can see that spontaneous oscillations in the number of infected persist, and are synchronized with corresponding oscillations in the effective number of strains and in the width of the distribution of strains in sequence space. In this systems, something analogous to the working regime of influenza appears to have been reached. One may also notice that the divergence between active strains, measured by the average Hamming distance, remains limited even if the average distance from the origin increases with time. The active strains show therefore ongoing change, but with a limited amount of divergence.

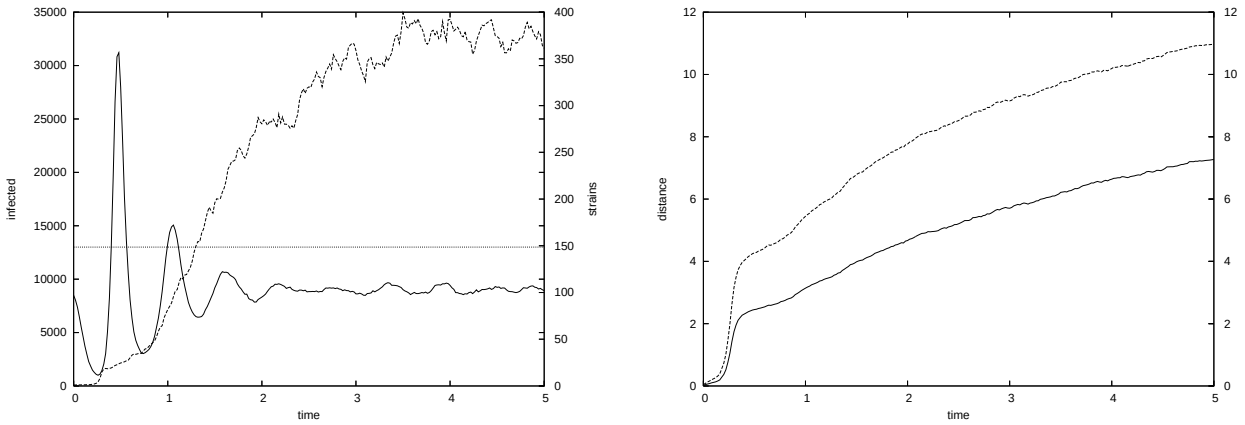

FIG. 3: Behavior of the system with *short immunity* but nonrandom infectivity. Infectivity $\beta = \beta_0 = 3$, short immunity duration $\eta = 0.75$. Other parameters as in fig. 1. Left: Continuous line (left axis): Number of infected vs. time. Horizontal line: expected number of infected according to eq. (6). Dashed line (right axis): Effective number of strains. Although the number of infected remains close to the equilibrium value I^*, the effective number of strains reaches a large value, corresponding to proliferation. Right: Continuous line: Average Hamming distance from the origin of the active strains. Dashed line: Average Hamming distance between active strains. One sees that the distance between active strains keeps increasing, witnessing their divergence. (With $L = 32$, the average distance in a random sample would be $d_{\rm H} = 16$.)

These results still hold if one introduces a small modulation with a period of one year in the infectivity [20], by letting, for each viral strain σ,

$$\beta_\sigma(t) = \beta_\sigma \left(1 + m_0 \sin(t/2\pi)\right). \qquad (7)$$

However, one can see that the characteristic time of the incidence ripples in our model correspond to a few months, as if it were essentially determined by the duration of the short immunity and of the illness, instead of by the viral strain turnover. Therefore a small modulation does little more than modulate the amplitude of the ripples, as shown in fig. 6.

V. DISCUSSION

In this paper we addressed the problem of understanding the dynamical mechanisms underlying antigenic drift of the influenza A virus. In particular we revisited the problem outlined in [5] of the existence of a constantly evolving well-defined strain giving rise to comb-like shape phylogenetic trees, i.e., to a constantly evolving viral population with comparatively narrow distribution in genetic space. We considered a minimal, individual based model that couples epidemic dynamics and viral evolution. Our main finding is that the absence of strain proliferation relates equally importantly to the large spectrum short-time cross-immunity emphasized in [5] and to heterogeneity in the effective viral infectivity. In our model we directly suppose that different strains have different values of the infectivity. Our results show that even a comparatively narrow distribution of infectivity, in combination with the increased competition due to the presence of the short immunity, is sufficient to lead to a "drifting quasispecies" behavior. We have also seen that, on the other hand, such a behavior has a very narrow range of stability, if any, if either the short immunity or the random infectivity is lacking, at least in a model of a comparatively large population without spatial structure, like the one we have considered. We expect, on the basis of Kimura's theory of selection in finite populations [18], that, as the population becomes larger and larger, the spread in viral infectivity needed to stabilize influenza behavior becomes narrower and narrower.

Perhaps obscured by the emphasis on short time immunity, a different mechanism was present in [5]. In that case the heterogeneity was provided by a non trivial "geographical distribution" of individuals. These were assumed to be randomly distributed on a two dimensional space. As an effect, the competition between different viral strains is enhanced, since some geographical locations acquire a leading role in spreading the disease, and the first strains to establish themselves in these locations acquire a standing advantage. However, the possibility that different strains are also characterized by different infectivities is quite natural and yields a realistic evolutionary dynamics. It appears that some heterogeneity and a mechanism for an enhanced competition among strains is all that is needed to reproduce the observed evolutionary pattern. Most probably, varying infectivities for different strains and a heterogeneous pattern of contacts among individuals in different communities both play a role in influenza spreading and viral evolution. We think that this point deserves further research. Understanding which contact and social patterns favor an increased effective infectivity could lead to more effective policies to keep under control influenza epidemics.

Finally, phylogenetic trees similar to the ones of the influenza virus have been observed in in-host HIV evolution [4]. The present work might be a stimulus to identify

the factors that play the role corresponding to short immunity and heterogeneous infectivities in that case.

Acknowledgments

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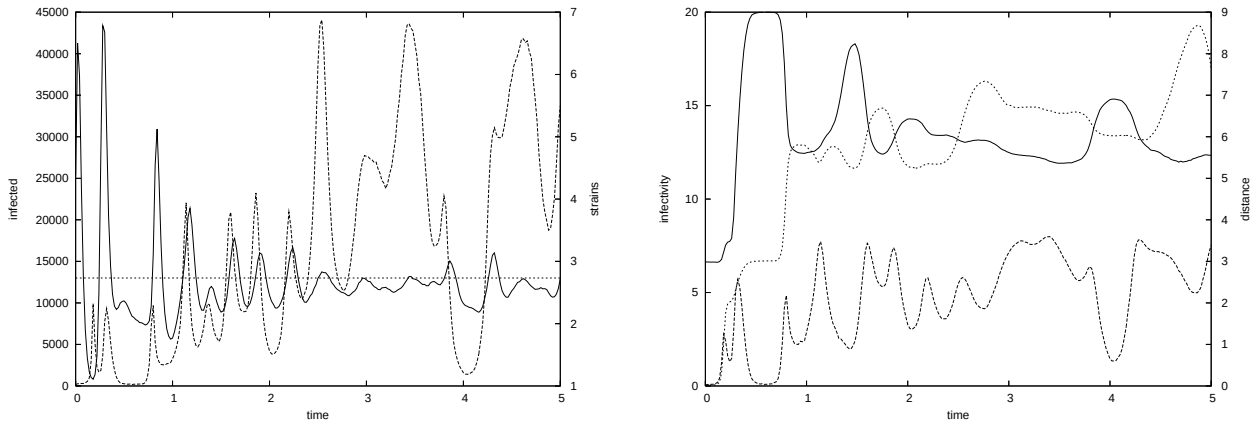

FIG. 4: Behavior of the system with randomly distributed infectivity and *short immunity*. Expected value of the infectivity $\beta_0 = 3$, parameter $k = 3$, range $r = 1$, short immunity duration $\eta = 0.75$. Other parameters as in fig. 1. Left: Continuous line (left axis): Number of infected vs. time. Horizontal line: expected number of infected according to eq. (6). Dashed line (right axis): Effective number of strains. Right: Continuous line (left axis): Average value of the infectivity. Dashed line (right axis): Average Hamming distance among active strains. Dotted line: Average Hamming distance from the origin for the active strains. Notice that the number of active strains and their mutual distance remain limited while exploring sequence space.

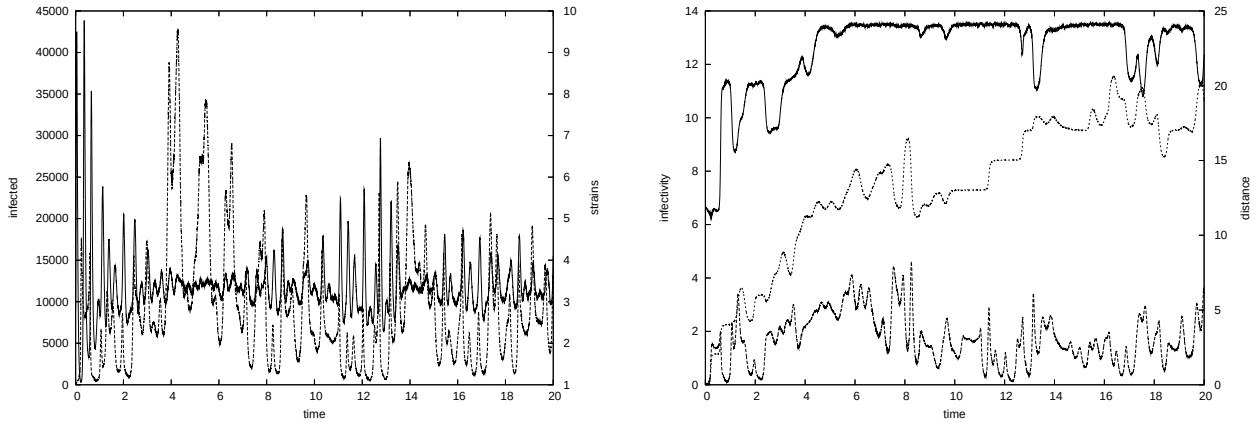

FIG. 5: Behavior of the slow version of the model with randomly distributed infectivity and *short immunity*. Expected value of the infectivity $\beta_0 = 3$, parameter $k = 3$, range $r = 1$, short immunity duration $\eta = 0.75$, genome length $L = 128$. Other parameters as in fig. 1. Left: Continuous line (left axis): Number of infected vs. time. Dashed line (right axis): Effective number of strains. Right: Continuous line (left axis): Average value of the infectivity. Dashed line (right axis): Average Hamming distance among active strains. Dotted line: Average Hamming distance from the origin for the active strains. The incidence ripples are more evident in this version since the correlations in the immunity state of the population are more correctly taken into account.

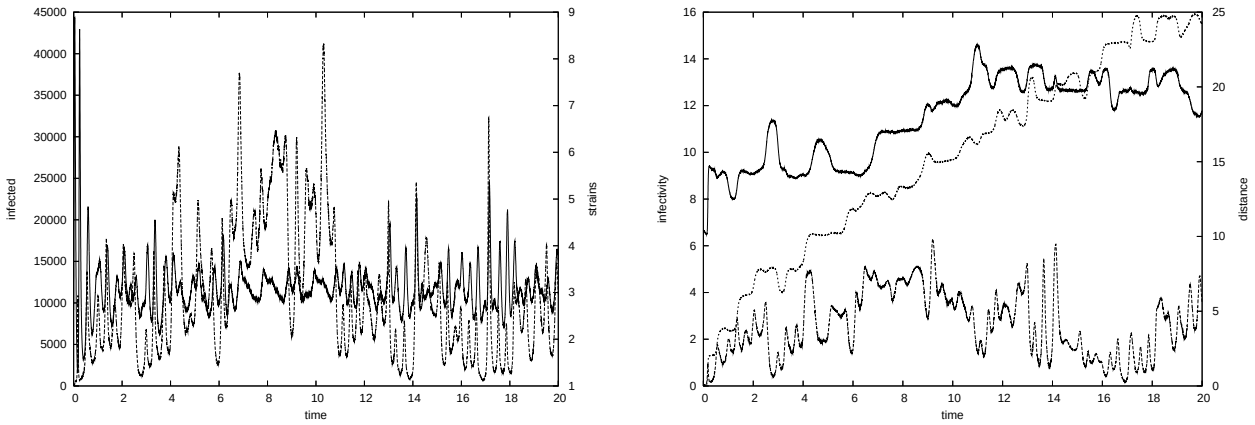

FIG. 6: Behavior of the slow version of the model with randomly distributed infectivity and *short immunity*, in the presence of a modulation of the infectivity according to eq. (7). Modulation $m_0 = 0.2$. Other parameters as in fig. 5. Left: Continuous line (left axis): Number of infected vs. time. Dashed line (right axis): Effective number of strains. Right: Continuous line (left axis): Average value of the infectivity. Dashed line (right axis): Average Hamming distance among active strains. Dotted line: Average Hamming distance from the origin for the active strains. The incidence ripples are more evident in this version since the correlations in the immunity state of the population are more correctly taken into account.